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ODM-204, a novel dual inhibitor of CYP17A1 and androgen receptor: Early results from phase I dose escalation in men with castration-resistant prostate cancer

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Abstract

Background: Most prostate cancer patients develop castration-resistant prostate cancer (CRPC) after androgen deprivation therapy treatment. CRPC growth is mediated by androgen receptor signalling driven by primary androgens synthesized largely by the CYP17A1 enzyme.

Objective: To evaluate the safety profile and dose limiting toxicities of ODM-204.

Design, setting, and participants: In this open, uncontrolled, non-randomised, multicentre, tolerability and pharmacokinetic first-in-man phase I dose escalation study, patients with metastatic CRPC were randomised to receive ODM-204 in sequential cohorts of 5 dose levels (i.e. 50, 100, 200, 300, and 500 mg twice daily) concomitantly with prednisone.

Intervention: ODM-204, a novel, orally administered investigational non-steroidal dual inhibitor of CYP17A1 and AR.

Outcome measurements and statistical analysis: ODM-204 plasma concentrations, serum testosterone, and prostate-specific antigen (PSA) levels were evaluated and imaging of lesions was performed.

Results and limitations: 60.9% of the twenty-three patients enrolled into the study experienced mild adverse effects (AEs) considered to be related to the study treatment, which were fatigue, increased/decreased appetite, nausea, asthenia, diarrhoea, and weight decrease. ODM-204 area under the curve (AUC_{0-12}) values increased dose-dependently until the 300 mg dose. The AUC

was lower on day 8 after repeated dosing compared to day 1 from the 200 mg dose upwards. Decreases in testosterone levels were seen with ODM-204 treatment confirming androgen deprivation. 13% of patients also demonstrated a greater than 50% decrease in PSA at week 12 and continued ODM-204 treatment for over a year.

Conclusions: ODM-204 was well tolerated up to the highest evaluated dose. There were decreases in both testosterone and PSA levels suggesting preliminary antitumor activity in the treatment of CRPC. The pharmacokinetic properties of the molecule, however, prevent further development.

Patient summary: This study looked at the safety of ODM-204, a novel dual inhibitor of CYP17A1 and the AR, in CRPC patients. ODM-204 treatment was found to be well tolerated and also reduced both serum testosterone and PSA levels, but the properties of the molecule prevent further development.

Introduction

The androgen receptor (AR) signalling pathway plays a major role in prostate cancer (PCa), and androgen deprivation therapy (ADT) by surgical or chemical castration is the standard treatment for patients with advanced PCa. After initial treatment response most of the patients, however, develop castration-resistant prostate cancer (CRPC) with a poor prognosis [1, 2]. In recent years, several clinical trials have shown that the castration-resistant growth is driven, to a large extent, by continued AR signalling, and that CRPC remains sensitive to androgens because of the sensitization and amplification of AR signalling [3-8]. Thus, hormonal manipulation with AR blockers, in addition to steroid biosynthesis inhibitors reducing the activation of the AR-mediated pathway [9], remain the core of CRPC treatment.

Although castration leads to very low levels of circulating testosterone, androgens are still present in prostate cancer tissues at clinically relevant concentrations that activate AR signalling and promote tumour growth [10]. The synthesis of the primary androgens testosterone and dihydrotestosterone (DHT) requires a cascade of oxidative enzymes, with one of the key enzymes being CYP17A1. Consequently, CYP17A1 inhibitors have been designed for the treatment of androgen-dependent PCa. The only CYP17A1-inhibitor currently approved for the treatment of CRPC, abiraterone, has been shown to exhibit a significant overall survival benefit in a post-chemotherapy phase III study, but some abiraterone-resistant tumours still continue to present persistent AR activation [11, 12]. Therefore, there is a clear rationale for developing

treatments that target CYP17A1 and AR together, as this may provide a more effective response than targeting either one alone.

Here, we present ODM-204, a novel, orally administered investigational non-steroidal dual inhibitor of CYP17A1 and AR that was shown to inhibit tumour growth in the murine VCaP CRPC xenograft model [13]. In this phase I dose escalation study, the safety profile of ODM-204 was shown to be satisfactory, but its pharmacokinetic profile would bring significant challenges on the development path.

Patients and Methods

Inclusion criteria

Eligible patients were males over the age of 18 with metastatic progressive CRPC with ongoing androgen deprivation (ADT) therapy by gonadotropin-releasing hormone (GnRH) agonist or antagonist, or bilateral orchiectomy, and serum testosterone level < 50 ng/dl at screening, as well as metastatic disease documented by bone scan, computed tomography or magnetic resonance imaging, and an Eastern Cooperative Oncology Group (ECOG) performance status 0-2. Disease progression was defined as rising PSA (progression defined by a minimum of two rising PSA levels with an interval of at least one week apart with the screening value ≥ 2 ng/ml), soft tissue disease progression as defined by RECIST 1.1 criteria, or 2 or more new bone lesions. Brain lesions were exclusionary. The patients had provided written informed consent and the study protocol was approved by independent ethics committees at each participating centre. The study was registered on ClinicalTrials.gov (NCT02344017).

Study design and treatment

This was an open, uncontrolled, non-randomised, multicentre, tolerability and pharmacokinetic first-in-man phase I dose escalation study of ODM-204 in patients with progressive metastatic CRPC. Escalating dose levels of ODM-204 (50, 100, 200, 300 and 500 mg twice daily) were administered in sequential cohorts of 3-6 subjects together with Prednison®. ODM-204 was taken orally twice a day with food (in the morning and evening) and 5 mg of Prednison® was

taken once or twice a day depending on the daily dose prior to study entry. The subjects who did not experience any dose-limiting toxicity (DLT) within 24 hours after the first dose continued ODM-204 treatment with b.i.d. dosing. DLTs were defined as any of the following toxicities graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) determined to be related to ODM-204 and occurring during the first 28 days of the study treatment: grade ≥ 3 toxicity, excluding haematological toxicities, nausea, vomiting and diarrhoea; grade ≥ 3 nausea, vomiting and diarrhoea uncontrolled with antiemetic and/or anti-diarrheal therapy; grade ≥ 3 haematological toxicity lasting for ≥ 7 days; grade ≥ 4 thrombocytopenia and neutropenia; other laboratory values of ≥ grade 3 which were judged clinically significant by the investigator, or any other toxicity which in the judgement of the investigator was viewed as a DLT. Once the safety of an administered dose was established, the next dose level was administered, and the patients with previous dose level were allowed to continue treatment with ODM-204 until progression or intolerable AEs. The next dose level was started after a minimum of 3 patients had completed 28 days of treatment and after safety review by the safety monitoring board (SMB).

Pharmacokinetic assessments

On day 1, blood samples were taken predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 and 24 h postdose after single dosing. On day 8 after repeated dosing, blood samples were taken predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 h. The plasma concentrations of ODM-204 were determined from the blood samples using liquid chromatography with tandem mass

spectrometry. AUC from time zero to 12 h, 24 h and infinity, maximum concentration (C_{max}), time to reach maximum concentration (t_{max}) and elimination half-life ($t_{½}$) were calculated using Phoenix WinNonlin software (Certara, Princeton, NJ, USA).

Antitumor activity

Serum total PSA concentration was determined every 4 weeks until 24 weeks and every 12 weeks thereafter. In case of PSA progression, a confirmatory test was obtained 3-4 weeks later. PSA response and progression were evaluated using PCWG2 criteria for PSA progression.

Testosterone concentrations were measured from blood samples on days 1, 8 and 29 after start of treatment, as well as on week 12, week 24 and every 12 weeks thereafter.

Chest, abdomen and pelvic CT or MRI (as per investigator's discretion) was performed at screening, week 12 and every 12 weeks thereafter to evaluate soft tissue disease progression as defined by RECIST 1.1 criteria.

Statistical considerations

Adverse events (AEs) reported after administration of the study treatment were classified by System organ classes (SOC) and preferred terms using the MedDRA dictionary. The number and proportion (%) of subjects experiencing each AE was tabulated. The AEs were graded by severity and causality. PK parameters were analysed after logarithm transformation and 95% confidence interval for the geometric mean will be calculated. Descriptive statistics for

continuous variables were: number of observations (N), mean (MEAN), standard deviation (SD), minimum (MIN), median, maximum (MAX). In PK variables also geometric mean (GMEAN) and coefficient of variation (CV) was calculated. Because log-normal distribution, the formula CV=100*square root(exp(variance of log-transformed data)-1) was used.

$$CV = 100 \times \sqrt{exp^{variance\ of\ log-transformed\ data} - 1}$$

Results

Patient characteristics and study drug exposure

In total, 23 patients with CRPC were enrolled into the study between 17 February, 2015 and 22 June, 2016, at four centres; three into the 50 mg twice daily dose level group, three into the 100 mg twice daily dose level group, six into the 200 mg twice daily dose level group, seven into the 300 mg twice daily dose level group, and four into the 500 mg twice daily dose level group. The cut-off date for the data included in this report was 21 December, 2017. Baseline demographics and disease characteristics are shown in Table 1. Median time on treatment was 12.1 weeks (0.3-71.7 weeks). Nine (39%) patients continued treatment for more than 12 weeks, and 4 (17%) patients were still receiving treatment at the time of data cut-off. *Adverse events*

Adverse events (AEs) were reported in all of the patients, and in 14 of the 23 patients (61%) these AEs were considered to be related to the study treatment. 22 (95%) of the patients suffered mild grade 1 AEs, 13 (57%) suffered moderate grade 2 AEs, and 7 (30%) suffered severe or life threatening grade 3-4 AEs. Of the serious AEs 3 (13%) were considered related to study treatment. The most common treatment related AEs were fatigue (22%), increased appetite (17%), nausea (17%), asthenia (9%), diarrhoea (9%), decreased appetite (9%), and weight decrease (9%). In 10 of the patients (43%) disease progression related AEs led to discontinuation from the study, while 6 (26%) patients were discontinued due to disease progression, 2 (9%) due to DLTs (drug hypersensitivity in one patient in the 300 mg cohort, and vomiting and nausea in

one patient in the 200 mg cohort), and 4 (17%) due to reasons classified as ‘other’. One patient in the 300 mg cohort died during the study period due to disease progression. In general, the occurrence of AEs was not deemed to be dose-dependent, as treatment related AEs, serious AEs, and discontinuations due to AEs were present in all the study groups in similar proportions. The most commonly reported AEs are shown in Table 2. *Pharmacokinetics*

Pharmacokinetic parameters for ODM-204 were determined on day 1 and day 8. On day 1 the $AUC_{0\text{-}12}$ of ODM-204 increased in a dose-dependent manner up to the 300 mg dose. At the 500 mg dose level, a slight decrease in $AUC_{0\text{-}12}$ was observed (Figure 1A). On day 8, $AUC_{0\text{-}12}$ increased up to the 300 mg twice daily dose with a slight decrease between the 100 mg and 200 mg twice daily doses and a remarkable decrease at the 500 mg twice daily dose level. Notably, the $AUC_{0\text{-}12}$ values were also greater on day 1 compared to day 8 from the 200 mg dose twice daily upwards. The C_{max} values on both day 1 and day 8 reflected in general the respective $AUC_{0\text{-}12}$ values (Figure 1B).*Testosterone changes*

Testosterone decreases of over 50% compared to baseline were observed in all of the studied doses after 8 days of ODM-204 treatment, with a decrease of over 75% present in some patients in the 50, 300 and 500 mg twice daily dose groups (Figure 2). However, the testosterone decrease was not dose-dependent and all cohorts (except the 50 mg cohort) included patients who did not present testosterone decrease. The majority of the maximum testosterone decreases, including all of the decreases over 50%, were seen at day 8, after which the testosterone levels started to increase back to the baseline in most patients. *PSA changes*

PSA decreases were seen in 7 (30%) patients at week 4, and the median decrease was 47% (2-99%). At week 12, 3 (13%) patients had PSA response with a 50% or higher reduction from baseline (Figure 3). Out of the seven patients that showed a PSA decrease at week 4, six continued ODM-204 treatment for at least 24 weeks without discontinuation due to an AE or disease progression, and three continued in the study for more than a year (Figure 4). Interestingly, one patient continued ODM-204 treatment for over 36 weeks without any initial PSA decrease, and three of the patients (patient ID: 2, 4, and 6; Figure 4) that had demonstrated initial PSA decrease were not discontinued from the study until several weeks after the point at which the PSA decrease had ended. The median time of ODM-204 treatment across cohorts was 12.14 weeks.

Imaging results of prostate lesions at week 12 showed that ODM-204 treatment resulted in a stable disease in one patient in the 50 and 200 mg twice daily group, and in two patients in the 500 mg twice daily group. Additionally, ODM-204 treatment also resulted in a stable disease regarding bone lesions in one patient in all of the studied dose cohorts, except in the 200 mg twice daily cohort where four patients were reported to have a stable disease bone response.

Discussion

In this first-in-man dose escalation trial ODM-204 was demonstrated to be generally well tolerated in CRPC patients, with doses up to 500 mg twice daily. One DLT occurred at the 300 mg twice daily cohort but a maximum tolerated dose was not reached. The dose escalation was discontinued at the 500 mg twice daily dose level because of decreased ODM-204 plasma concentrations at the higher dose levels after repeated dosing on day 8 compared to single dosing on day 1. The most common treatment-related AEs, fatigue, increased/decreased appetite, nausea, asthenia, diarrhoea, and weight decrease, were generally of grade 1 and 2 in severity and without significant clinical consequence. The AE profile did not differ between dose levels. These AEs are in line with previous observations showing that AR inhibitors such as enzalutamide are associated with fatigue and gastrointestinal events [14, 15]. Interestingly, ODM-204 treatment did not demonstrate cardiac adverse events, which have been associated with the CYP17A1 inhibitor abiraterone [14]. Additionally, the incidence and severity did not appear to be directly dose-related nor related to differences in the ODM-204 plasma concentration.

The interpretation of antitumor activity can be difficult in the setting of a phase I trial given that cohorts are small and doses variable, but the current study did provide some indication of the efficacy of ODM-204. Firstly, ODM-204 treatment resulted in a decrease of serum testosterone levels in most of the patients in all of the studied dose cohorts. As serum testosterone level monitoring is commonly used to verify response to ADT [16], this confirms the androgen

deprivation effect of ODM-204. Secondly, serum PSA levels were also decreased by ODM-204 treatment in 30% of the patients with 13% showing a decrease of over 50% compared to the baseline. Thirdly, the imaging results showed that ODM-204 treatment resulted in a stable disease in four patients at week 12 as well as the arrest of bone lesion progressing in at least one patient in each dose cohort. Importantly, the patients demonstrating over 50% decrease in PSA continued ODM-204 treatment for over a year without discontinuation due to an AE or disease progression, which is an encouraging outcome. Taken together, these data suggest that dual inhibition of CYP17A1 and AR could be a valuable mechanism for treatment of prostate cancer patients [17].

Interestingly, the AUC (from the 200 mg dose upwards) and C_{max} values of ODM-204 were unexpectedly greater on day 1 compared to day 8, contrary to what has been observed in the nonclinical studies in monkeys. At the 500 mg dose level, decreases in AUC values were also observed on both day 1 and day 8 suggesting a decrease in the steady state plasma concentration of ODM-204. This effect may be related to an induction of an elimination route caused by ODM-204, and it seems to become pronounced especially at the higher doses after an eight-day exposure to ODM-204. If so, the patients having less decrease in steady-state plasma concentrations should have better outcomes, and interestingly the patient (dosed 300mg twice a day) that had both the highest plasma concentrations and the lowest decrease in AUC by day 8 used the CYP3A4 inhibitor ezetimibe [18]. Hence, the pharmacokinetic properties make the further development of the molecule challenging.

In conclusion, ODM-204 demonstrated an acceptable safety profile up to the highest tested dose 500 mg twice daily as well as preliminary antitumor activity in some patients. Based on this study, no new trials are currently being planned with ODM-204.

Acknowledgments

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Figure Legends

Table 1. Patient characteristics at baseline.

Table 2. Most common adverse events by dose (subject count and percentage).

Figure 1. Pharmacokinetics of ODM-204. A) AUC_{0-12} and B) C_{max} versus dose, mean+SD.

Figure 2. Maximum testosterone changes during the first 4 weeks compared to baseline.

Figure 3. Maximum PSA change (%) from baseline during 12 weeks. PSA = prostate-specific antigen.

Figure 4. Duration of ODM-204 treatment. Time in weeks spent in the study without discontinuation due to an AE or disease progression. Blue bars denote patients that demonstrated PSA decrease, and red bars denote patients that did not.

Tables and figures

Table 1. Patient characteristics at baseline.

Characteristics	Total daily dose[a]					Total
	100 mg (*N* = 3)	200 mg (*N* = 3)	400 mg (*N* = 6)	600 mg (*N* = 7)	1000 mg (*N* = 4)	(*N* = 23)
Median age (range), years	74 (66–76)	70 (59–77)	68.5 (61–75)	69 (57–84)	71 (66–74)	70 (57–84)
ECOG, *n* (%)						
0	1 (33)	1 (33)	4 (67)	3 (43)	3 (75)	12 (52)
1	2 (67)	2 (67)	2 (33)	4 (57)	1 (25)	11 (48)
BMI						
Median	25.1	30.8	31.5	29.7	27.4	29.8
(kg/m^2, min–max)	(24–32)	(26–31)	(25–40)	(21–32)	(25–37)	(21–40)
PSA						
Median	149.6	50.0	26.7	94.4	19.1	46.5
(ng/ml, min–max)	(68.3–162.3)	(14.5–210.9)	(5.5–249.6)	(7.2–194.7)	(0.7–36.5)	(0.7–249.6)
Gleason score						
Low [2-4]	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	1 (4)
Medium [5-7]	1 (33)	0 (0)	3 (50)	3 (43)	1 (25)	8 (35)
High [8-10]	2 (67)	2 (67)	3 (50)	3 (43)	3 (75)	13 (57)
Previous therapies, *n* (%)						
Chemotherapy	1 (33)	2 (67)	2 (33)	5 (71)	3 (75)	10 (43)
Abiraterone	0 (0)	1 (33)	2 (33)	2 (29)	3 (75)	8 (35)
Enzalutamide	0 (0)	1 (33)	2 (33)	5 (71)	3 (75)	4 (17)

[a]Administered twice daily.

Table 2. Most common adverse events by dose (subject count and percentage).

Adverse event, *n* (%)	Daily total dose[a]					Total
	100 mg (*N* = 3)	200 mg (*N* = 3)	400 mg (*N* = 6)	600 mg (*N* = 7)	1000 mg (*N* = 4)	(*N* = 23)
Decreased appetite		2 (67)		3 (43)	1 (25)	6 (26)
Fatigue	1 (33)	1 (33)	2 (33)	1 (14)	1 (25)	6 (26)
Nausea		1 (33)	2 (33)	2 (29)	1 (25)	6 (26)
Diarrhoea		1 (33)	2 (33)	2 (29)		5 (22)
Vomiting		1 (33)	1 (17)	2 (29)	1 (25)	5 (22)
Asthenia		1 (33)		3 (43)		4 (17)
Constipation		1 (33)	1 (17)	1 (14)	1 (25)	4 (17)
Insomnia			1 (17)	2 (29)	1 (25)	4 (17)
Weight decrease			1 (17)	1 (14)	2 (50)	4 (17)
Abdominal pain				2 (29)	1 (25)	3 (13)
Back pain			1 (17)		2 (50)	3 (13)
Blood potassium decrease			1 (17)	1 (14)	1 (25)	3 (13)
Depressed mood		1 (33)		1 (14)	1 (25)	3 (13)
Pain in extremity	1 (33)	1 (33)	1 (17)			3 (13)

[a]Administered twice daily.

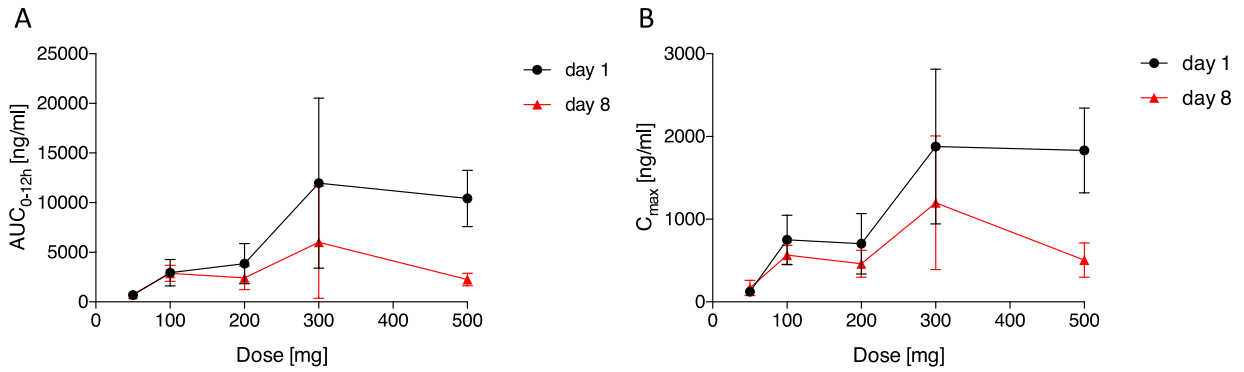


Figure 1. Pharmacokinetics of ODM-204. A) $AUC_{0\text{-}12}$ and B) C_{max} versus dose, mean+SD.

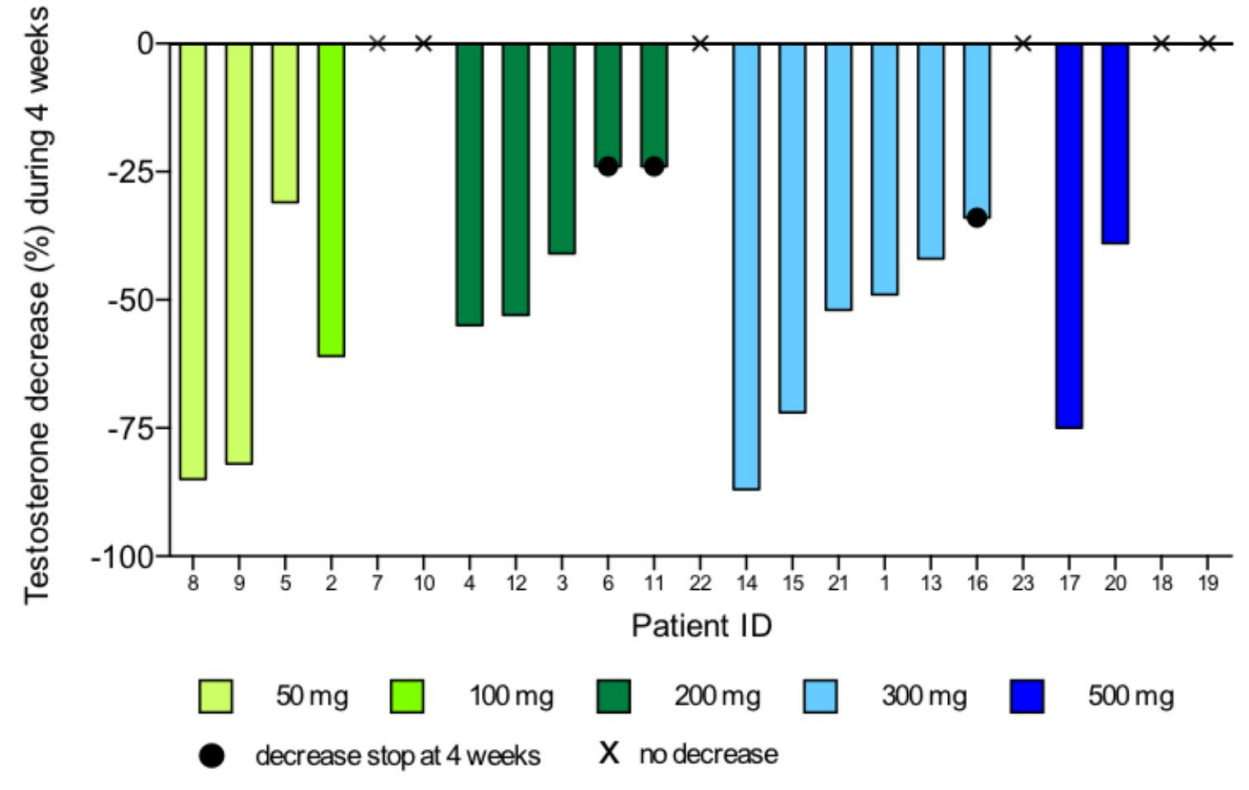


Figure 2. Maximum testosterone changes during the first 4 weeks compared to baseline.

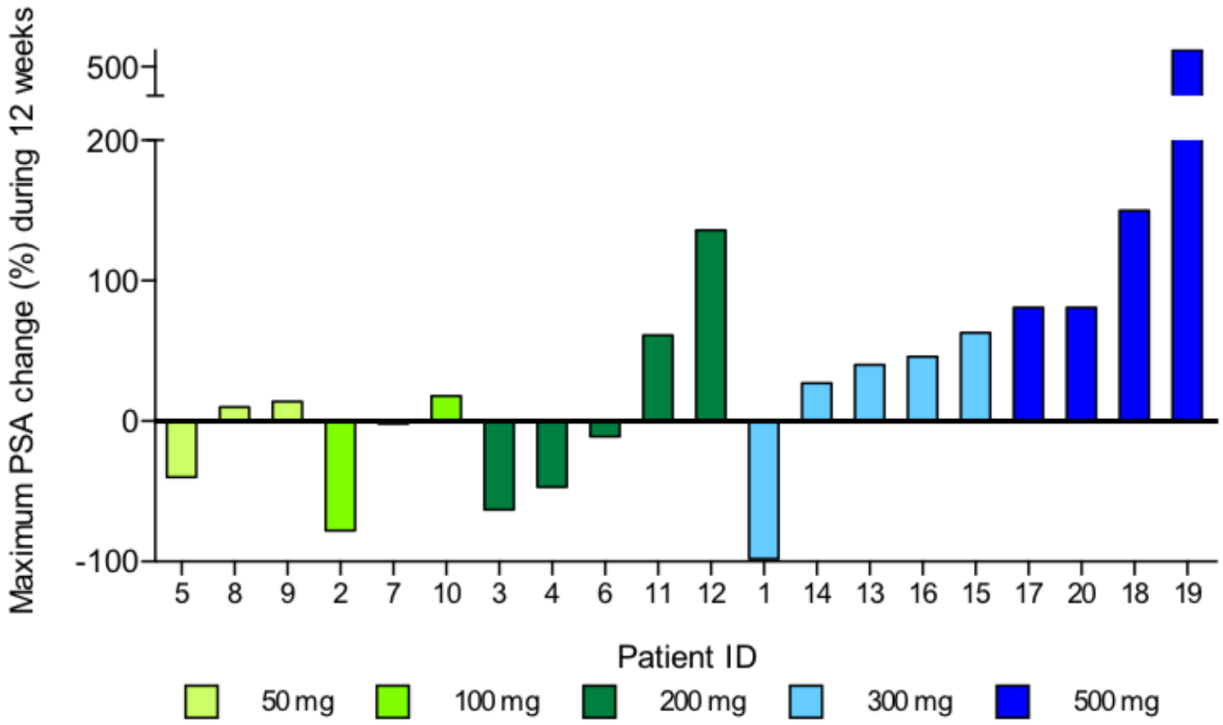
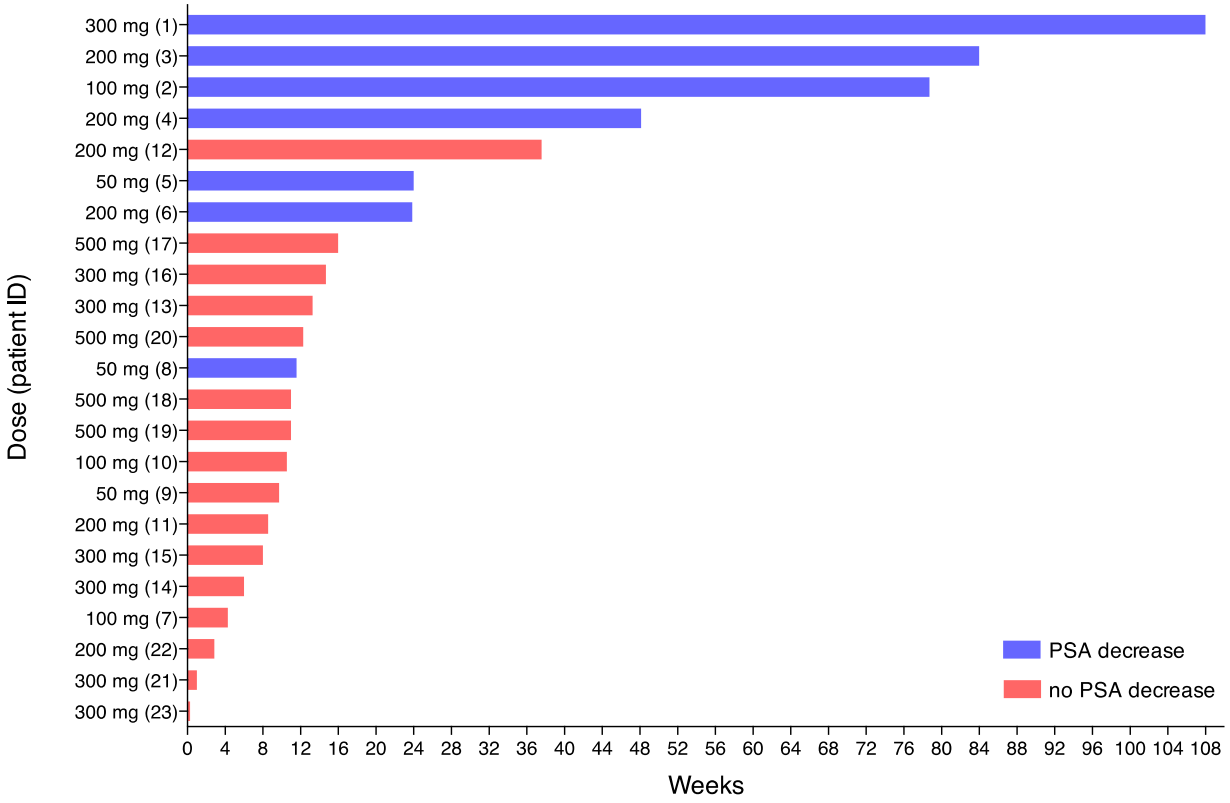


Figure 3. Maximum PSA change (%) from baseline during 12 weeks. PSA = prostate-specific antigen.



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The authors listed below have made substantial contributions to the intellectual content of the paper in the various sections described below.

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_ conception and design	KF, MM, PB
_ acquisition of data	KP, PB, RJ, EV, KF, CM
_ analysis and interpretation of data	KP, PB, RJ, EV, PN, AV, RO, PP, MM, KF, CM
_ drafting of the manuscript	KP, PB, PP, MM, KF, CM
_ critical revision of the manuscript for important intellectual content	KP, PB, MM, CM
_ statistical analysis	PP
_ obtaining funding	PN, AV, RO, PP, MM
_ administrative, technical, or material support	PN, AV, PP, MM
_ supervision	PB, MM, KF, CM
_ other (specify)	

Financial Disclosure

☐ None of the contributing authors have any conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

OR

☒ I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: *(please list all conflict of interest with the relevant author's name):*

Dr. Peltola reports personal fees from Orion Pharma, BMS, Pfizer, Roche, MSD, and Ipsen outside the submitted work, and is a stock holder in Faron Pharmaceuticals. Dr. Bono reports

honoraria from Orion Pharma during the conduct of the study, and honoraria from Pfizer, MSD, BMS, Novartis and Ipsen outside the submitted work. Dr. Nykänen, Dr. Vuorela, Dr. Oksala, Dr. Pohjanjousi and Dr. Mustonen are employees of Orion Corporation Orion Pharma. Dr. Fizazi reports participation to advisory boards and honoraria from Amgen, Astellas, Bayer, Jansen, Sanofi, and Orion outside the submitted work. Dr. Massard reports participation to advisory boards, payment for speaker bureau, investigator from Amgen, Astellas, Astra Zeneca, Bayer, Celgene, Genentech, Ipsen, Jansen, Lilly, Novartis, Pfizer, Roche, Sanofi, and Orion outside the submitted work. Dr. Jones has declared no conflicts of interest.

Funding Support and Role of the Sponsor

☒ I certify that all funding, other financial support, and material support for this research and/or work are clearly identified in the manuscript.

The name of the organization or organizations which had a role in sponsoring the data and material in the study are also listed below:

Orion Corporation Orion Pharma.

All funding or other financial support, and material support for this research and/or work, if any, are clearly identified hereunder:

The specific role of the funding organization or sponsor is as follows:

☒ Design and conduct of the study
☒ Collection of the data
☒ Management of the data
☒ Analysis
☒ Interpretation of the data
☒ Preparation
☒ Review
☒ Approval of the manuscript

OR

☐ No funding or other financial support was received.

Acknowledgment Statement

This corresponding author certifies that:
• all persons who have made substantial contributions to the work reported in this manuscript (eg, data collection, analysis, or writing or editing assistance) but who do not fulfill the authorship criteria are named with their specific contributions in an Acknowledgment in the manuscript.
• all persons named in the Acknowledgment have provided written permission to be named.
• if an Acknowledgment section is not included, no other persons have made substantial contributions to this manuscript.
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After completing all the required fields above, this form must be uploaded with the manuscript and other required fields at the time of electronic submission.

18th May 2018

MIKA MUSTONEN

Take home message

In a phase I dose-escalation study, a dual inhibitor of CYP17A1 and the AR, ODM-204, was well tolerated and demonstrated antitumor activity by decreasing serum testosterone and PSA levels in patients with CRPC. The pharmacokinetic properties, however, prevent further development.

Figure 1

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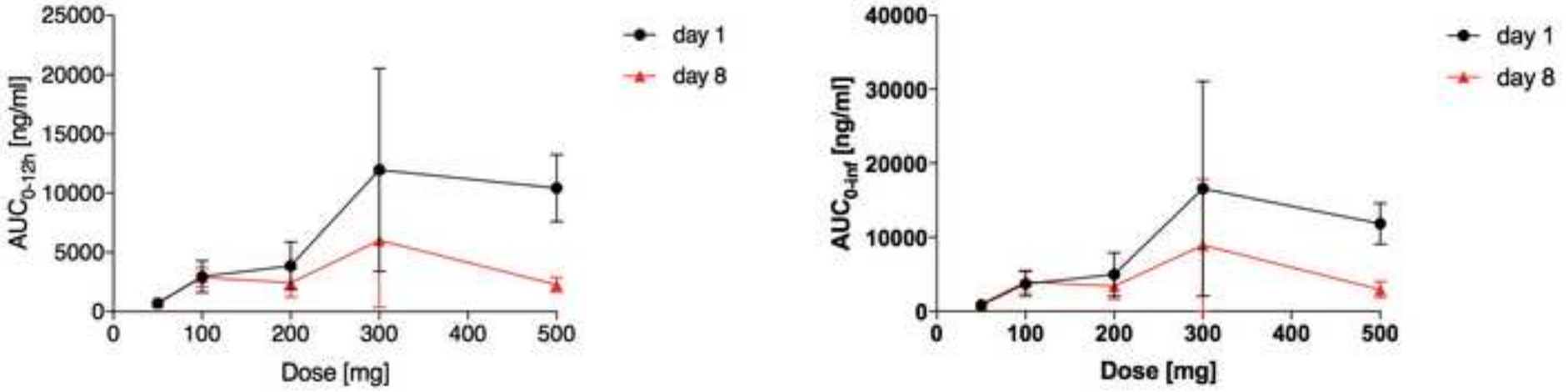

Figure 2

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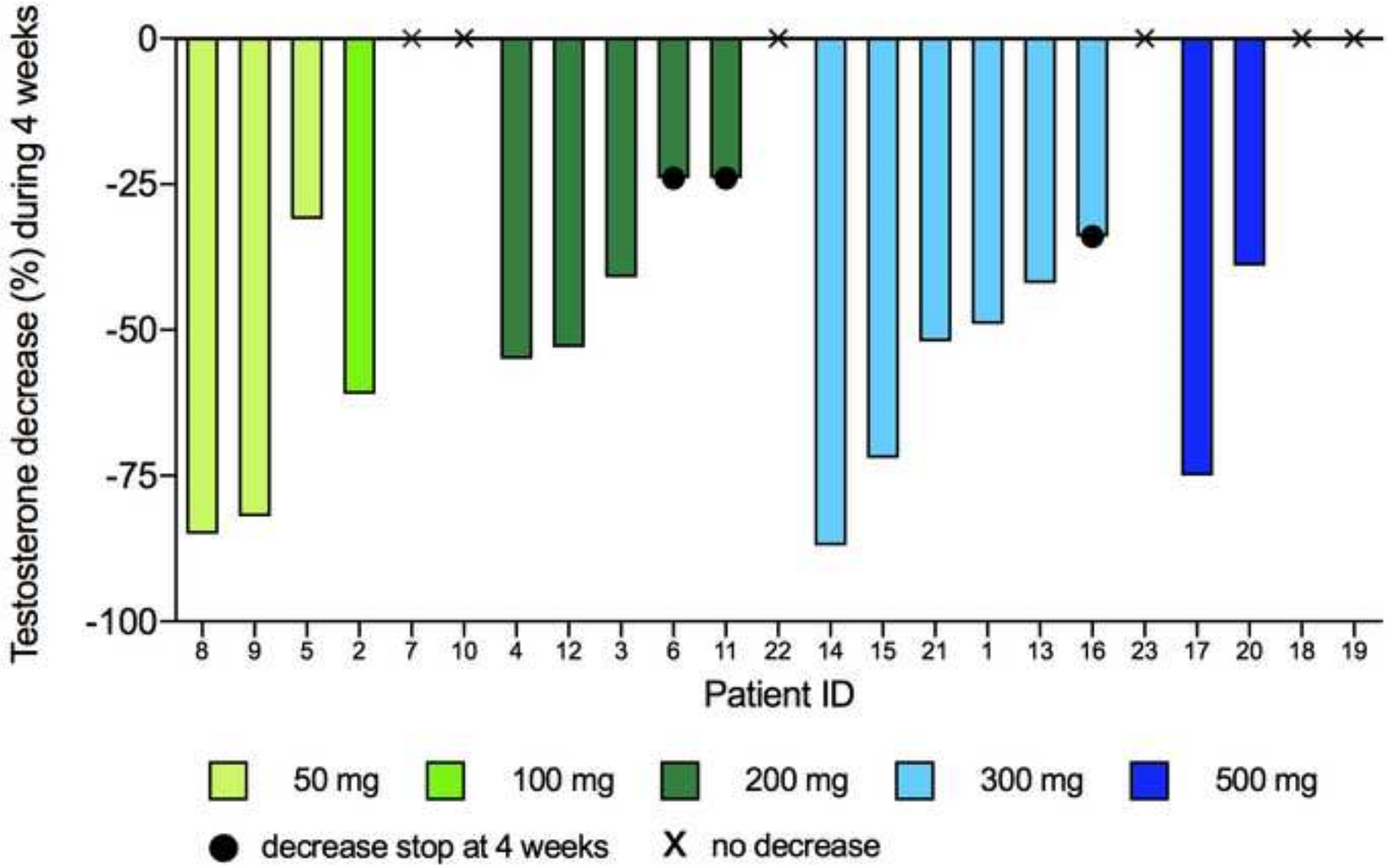

Figure 3

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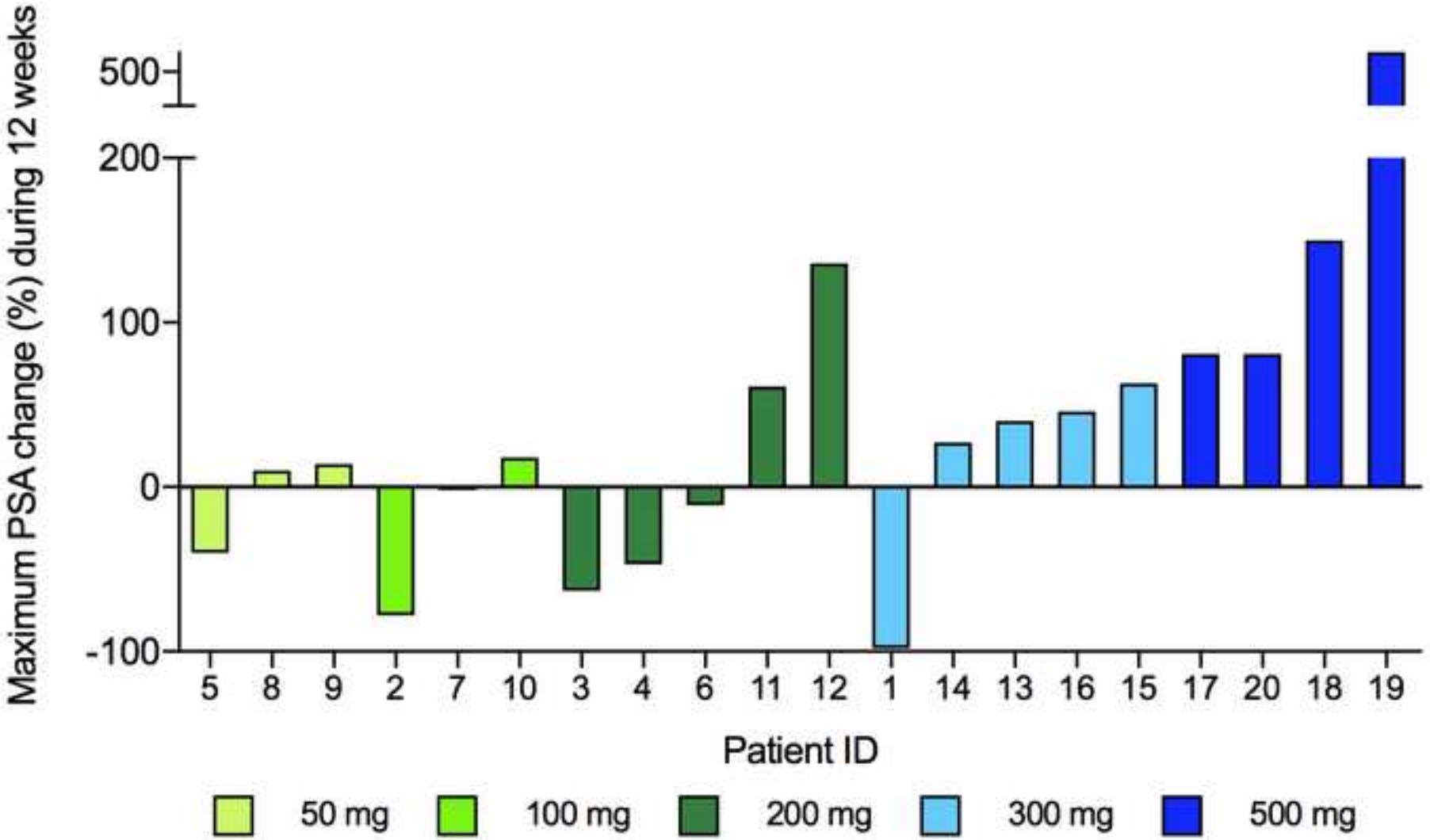

Figure 4

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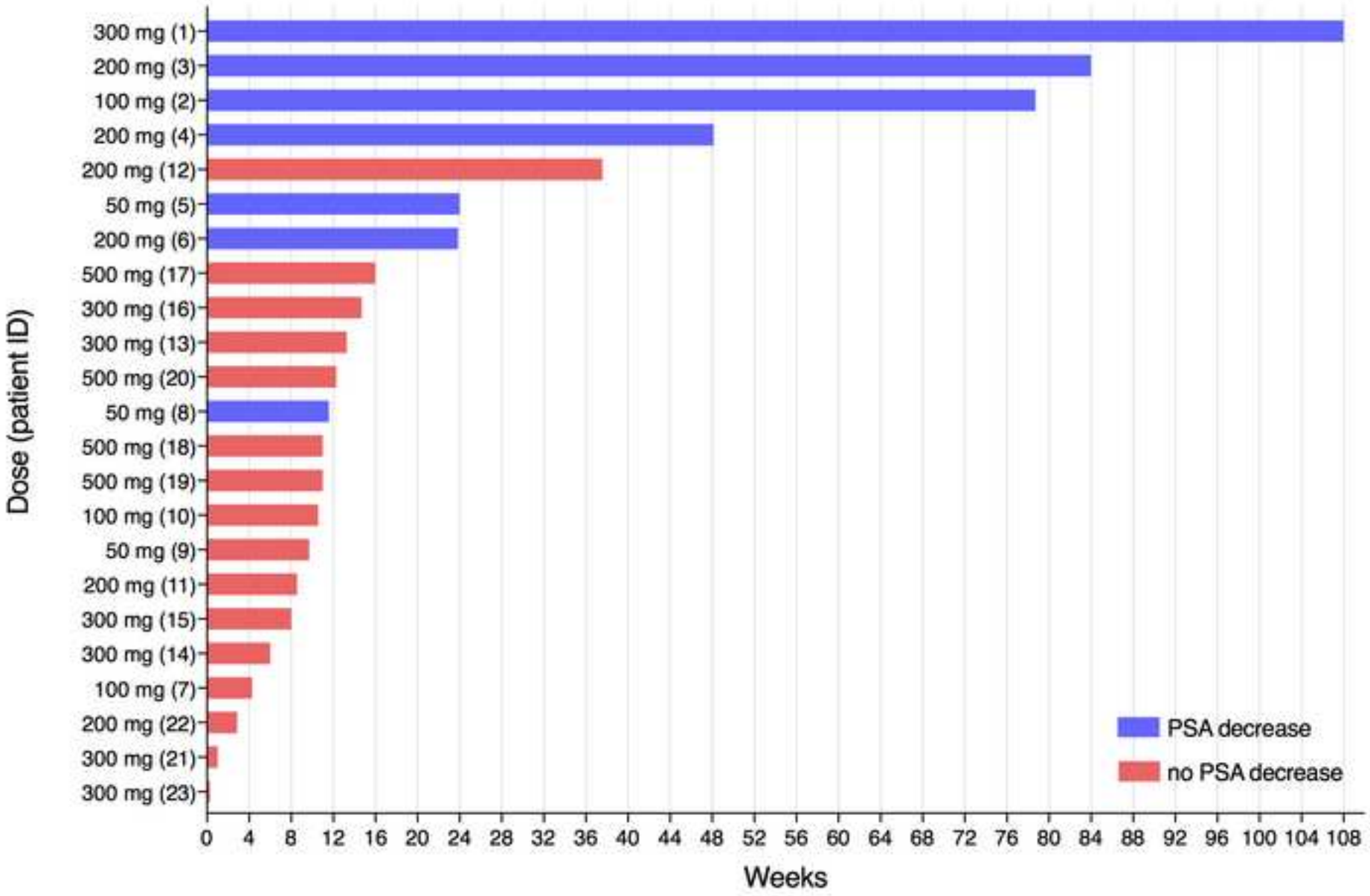

Table 1. Patient characteristics at baseline.

Characteristics	Total daily dose[a]					Total
	100 mg (*N* = 3)	200 mg (*N* = 3)	400 mg (*N* = 6)	600 mg (*N* = 7)	1000 mg (*N* = 4)	(*N* = 23)
Median age (range), years	74 (66–76)	70 (59–77)	68.5 (61–75)	69 (57–84)	71 (66–74)	70 (57–84)
ECOG, *n* (%)						
0	1 (33)	1 (33)	4 (67)	3 (43)	3 (75)	12 (52)
1	2 (67)	2 (67)	2 (33)	4 (57)	1 (25)	11 (48)
BMI						
Median	25.1	30.8	31.5	29.7	27.4	29.8
(kg/m^2, min–max)	(24–32)	(26–31)	(25–40)	(21–32)	(25–37)	(21–40)
PSA						
Median	149.6	50.0	26.7	94.4	19.1	46.5
(ng/ml, min–max)	(68.3–162.3)	(14.5–210.9)	(5.5–249.6)	(7.2–194.7)	(0.7–36.5)	(0.7–249.6)
Gleason score						
Low [2-4]	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	1 (4)
Medium [5-7]	1 (33)	0 (0)	3 (50)	3 (43)	1 (25)	8 (35)
High [8-10]	2 (67)	2 (67)	3 (50)	3 (43)	3 (75)	13 (57)
Previous therapies, *n* (%)						
Chemotherapy	1 (33)	2 (67)	2 (33)	5 (71)	3 (75)	10 (43)
Abiraterone	0 (0)	1 (33)	2 (33)	2 (29)	3 (75)	8 (35)
Enzalutamide	0 (0)	1 (33)	2 (33)	5 (71)	3 (75)	4 (17)

[a]Administered twice daily.

Table 2. Most common adverse events by dose (subject count and percentage).

Adverse event, *n* (%)	Daily total dose[a]					Total
	100 mg (*N* = 3)	200 mg (*N* = 3)	400 mg (*N* = 6)	600 mg (*N* = 7)	1000 mg (*N* = 4)	(*N* = 23)
Decreased appetite		2 (67)		3 (43)	1 (25)	6 (26)
Fatigue	1 (33)	1 (33)	2 (33)	1 (14)	1 (25)	6 (26)
Nausea		1 (33)	2 (33)	2 (29)	1 (25)	6 (26)
Diarrhoea		1 (33)	2 (33)	2 (29)		5 (22)
Vomiting		1 (33)	1 (17)	2 (29)	1 (25)	5 (22)
Asthenia		1 (33)		3 (43)		4 (17)
Constipation		1 (33)	1 (17)	1 (14)	1 (25)	4 (17)
Insomnia			1 (17)	2 (29)	1 (25)	4 (17)
Weight decrease			1 (17)	1 (14)	2 (50)	4 (17)
Abdominal pain				2 (29)	1 (25)	3 (13)
Back pain			1 (17)		2 (50)	3 (13)
Blood potassium decrease			1 (17)	1 (14)	1 (25)	3 (13)
Depressed mood		1 (33)		1 (14)	1 (25)	3 (13)
Pain in extremity	1 (33)	1 (33)	1 (17)			3 (13)

[a]Administered twice daily.